GENE THERAPY ADVISORY COMMITTEE

FOURTH ANNUAL REPORT

JANUARY 1997 – DECEMBER 1997

Health Departments of the United Kingdom
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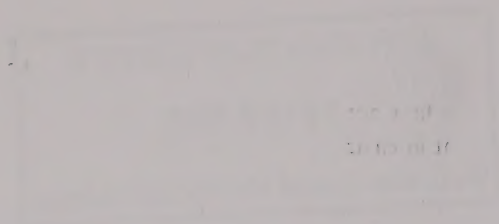
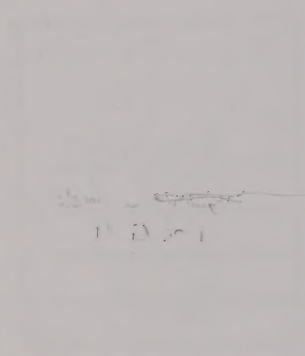




FOREWORD

Key features of this fourth year[1] of GTAC's activity have been expansion and diversity. Whether in terms of protocol review or GTAC's interface role with the public and scientific communities, 1997 has been a progressive and fruitful year.

Scientists and clinicians around the world, despite being somewhat chastened at the end of 1996[4], approached 1997 with renewed vigour, diversifying techniques of gene transfer and increasing the scope and numbers of clinical trials. On the stock markets encouraging signs were also seen indicating that gene therapy is moving into an expansive phase.

In the UK a doubling in 1997 of the number of new applications, and a continued increase in applicants wishing to amend approved protocols attested to this increase in activity. Research into cancer therapeutics, in keeping with the trend set in 1996, has been the main beneficiary. However, whilst scientific advancements gained from these trials may benefit the whole field, it is important that the rarer single gene disorders should not be overlooked.

Last March GTAC held a public Workshop entitled "Gene Therapy: Myth and Reality; Hype and Practicality" at the Central Public Health Laboratory, London. The aims were to assess the achievements of gene therapy, its future development and potential barriers to advancement.

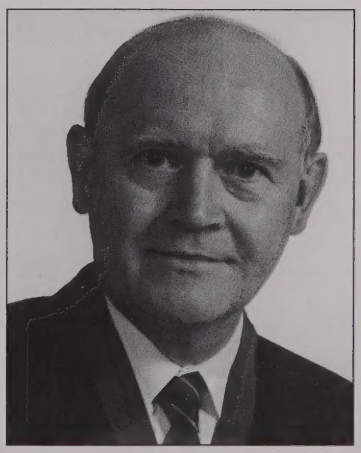
I wish to take this opportunity to thank all those whose participation made this first Workshop a resounding success. It is planned that, either by further consultation or by follow-up smaller workshops, some of the issues identified[2] will be addressed in 1998.

In such a rapidly evolving field as human gene transfer, GTAC felt that it was important to establish a standing subgroup whose remit would be to examine the potential clinical and ethical implications of new gene technologies. The group met for the first time in November 1997 to examine *in utero* gene therapy. A report on its conclusions is awaited.

The UK saw the first approval of a Herpes Simplex Virus (HSV) agent in clinical trials in December 1996. HSV has the potential to be one of the most exciting advances in neural gene therapy.

Last Spring GTAC established an expert advisory group[3] who met, with myself, to elaborate and advance a report to assist gene therapists working with HSV. Consultation on the report is now complete. The many helpful remarks and suggestions have been integrated. With our colleagues at the MCA we hope to continue to take this initiative forward in 1998.

Finally, it gives me immense pleasure to welcome Professor Patrick Johnston who joined GTAC during 1997.



Professor Norman C. Nevin
1998

[1] Previous GTAC work is reported in the First[1], Second[2] and Third[3] Annual Reports.

[2] See "Proceedings" document, available on the Internet on DH Homepage (http://www.open.gov.uk/doh/genetics/htm), or from the Genetics Secretariat.

[3] See Annex 3.

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ANNEXES

SECTION 1 - PROTOCOLS CONSIDERED BY GTAC (1997)

1.1 GTAC met five times during 1997 and assessed a total of 10 protocols in committee. GTAC was satisfied in principle, subject to conditions, for 6 protocols to proceed. Following the Committee's request for resubmission, 3 protocols are still under consideration and 1 protocol has been withdrawn.

1.2 In addition the Committee received a number of requests from investigators to make amendments to existing approved gene therapy protocols. Whenever appropriate these were dealt with either by agreement with the Chairman or by postal circulation to Committee members. These are recorded in detail in Section 2.

GLIOBLASTOMA

1.3 Worldwide, serious *neurological*[1] disease affects about 3% of the human population. In the UK approximately 4,000-5,000 patients with brain tumours are diagnosed each year. 50% of primary brain tumours are gliomas. The most common glioma is glioblastoma multiforme.

1.4 Current treatments for glioblastoma (radiotherapy, chemotherapy, surgery) are *palliative* and rarely alter the long term prognosis. Patients with glioblastoma have a very poor prognosis despite surgical removal of their tumours and aggressive post-operative radiotherapy. Studies suggest an average survival of 9-10 months. Five year survival is extremely rare.

To conduct a clinical trial in the UK with SDZ GLI 328, a gene therapy product, in patients with newly diagnosed, previously untreated glioblastoma - Institute of Neurological Sciences, Southern General Hospital, Glasgow (GTAC 019)

1.5 The application to GTAC was part of a multinational trial of a *retroviral* system of gene delivery in patients with glioblastoma primary brain tumours. The protocol proposed a novel approach to gene delivery. Instead of introducing a viral *vector* carrying the desired gene as we have seen in previous cancer studies, the vector producer cells (VPCs) - a cloned packaging cell line of mouse origin - were to be placed directly at the site of the resected brain tumour; the retroviral vectors made by the VPCs are expected to enter the remaining rapidly dividing tumour cells. Such an approach to gene therapy had been carried out in a number of trials primarily in the USA, and a number of European countries.

1.6 The gene of interest being transferred by the retroviral vector is thymidine kinase (TK) - an *enzyme* originated from Herpes Simplex virus - which can convert a *prodrug*. Prodrugs are relatively inert compounds that are converted to an active or toxic form in the body. The TK enzyme converts the prodrug ganciclovir to the toxic form, which will kill the TK containing tumour cells. The TK gene can only be transferred to rapidly dividing cells - and in the brain, these would in principle be cancerous cells. VPCs would not be expected to remain viable for more than a few days. However in this time they would produce, in situ the retroviral virus that transfers the TK gene.

1.7 Unlike the earlier trials in which gene therapy was carried out in patients with tumour recurrence and who had received and failed "conventional" treatment, including surgery and radiotherapy, the protocol was to recruit newly diagnosed, previously untreated glioblastoma patients. Patients would be divided into two groups - both would receive "conventional" therapy, but one group will also receive gene therapy.

[1] Words in *italics* appear in the Glossary: Section 10

1.8 GTAC first considered this protocol at its meeting in October 1996. The Committee recognised that the trial raised a number of new ethical and scientific questions due to the use of *murine* cell lines. GTAC decided to defer consideration until its March 1997 meeting and to seek advice from two sister committees - the Advisory Committee on Dangerous Pathogens (ACDP) and the UK Xenotransplantation Interim Regulatory Authority (UKXIRA).

1.9 The report from ACDP concluded that, given the cell line's long track record in both animal and human clinical trials, it carried one of the lowest risks of any animal line in terms of previously unreported or unrecognised virus. Moreover the risk of any infection arising that could harm the patient was considered to be much lower than the general risks of the procedures involved in the study. In terms of infection beyond the patient to a third party this risk was also estimated to be very low.

1.10 UKXIRA, recognising that the use of animal cells may be construed as a form of xenotransplantation, acknowledged the fundamental differences between the use of *xenogenic* whole organ transplantation and use of VPC in gene therapy.

1.11 UKXIRA agreed with the findings of the ACDP on the infection risks posed. The committee expressed the wish to be kept informed of progress in this trial.

1.12 At the March 1997 GTAC meeting advice from ACDP and UKXIRA, and further information provided by the proposers, was considered; and in July 1997 GTAC gave conditional approval to the research trial. In particular GTAC requested a change in the eligibility criteria to restrict the patient group to those newly diagnosed glioblastoma patients considered unsuitable for conventional treatment. In addition GTAC requested the establishment of a Safety Data Monitoring Committee that would report directly to GTAC and a number of changes to the written patient information.

GASTROINTESTINAL CANCER/ MALIGNANT ASCITES

1.13 There are approximately 53,000 new cases of gastrointestinal (GI) cancer per year in the UK resulting in about 44,000 deaths (~ 25% of all cancer deaths). Malignant *ascites* (abnormal accumulation of fluid in the abdominal cavity) is a common feature of patients with advanced GI cancer. Ascites occur in approximately 15% of cases.

1.14 The most frequent of all cancer-related genetic change involves *mutations* of the p53 *tumour suppressor* gene. The normal gene encodes a nuclear protein which is thought to stop *tumourigenicity* by regulating cell *proliferation*. The loss of p53 function is therefore implicated in unrestrained cellular growth and malignancy. About 50% of all cancers, and approximately 40 to 80% of all GI cancers, have defective p53 function.

1.15 Treatment is focused on palliation of symptoms. Available treatments include repeated paracentesis (surgical puncture or tapping), surgery, chemotherapy or *shunts*. An average survival rate for patients with newly diagnosed malignant ascites is between 2-6 months, depending on the type of tumour.

To conduct a clinical trial in the UK with Ad-5 CMV-p53 vector in patients with ascites formation - The Royal Marsden Hospital, London (GTAC 020)

1.16 The goal of the protocol was to express the p53 gene at the site of the malignant ascites formation (the abdominal or peritoneal cavity) by the introduction of a *recombinant adenoviral vector* Ad-5 CMV-p53 containing the human form of the tumour suppressor gene.

1.17 *Adenoviruses* are common DNA containing viruses found in the respiratory tract where they can cause infections. This is the second p53 adenoviral trial to be proposed in the UK. The first proposal was approved by GTAC to take place at the Royal Marsden Hospital in

September 1996[3]. Experimental data demonstrating safety and possible efficacy of the adenoviral p53 gene delivery system comes mainly from colorectal or head and neck cancer protocols. These studies of p53 deficient or mutant human tumour lines have indicated that restoration of p53 activity can result in the suppression of tumour growth.

1.18 In the new Royal Marsden Hospital trial, Ad-5 CMV-p53 is to be administered to adult male or female patients presenting with malignant ascites due to GI cancers or unknown primary cancers. Up to 24 patients are to be recruited.

1.19 GTAC gave approval in April 1997 to the trial subject to a restriction that only patients with primary tumours of known origin be recruited. In addition the Committee required further details on immunological testing and prior evaluation of p53 status.

BREAST CANCER

1.20 Breast cancer remains the leading cause of death from cancer in England in women aged over 35. The number of new patients with breast cancer in the UK is around 25,000 cases a year. In 1994 breast cancer caused 19.2% of all cancer deaths in women and 16% of all cancer deaths in women over 65.

1.21 Early diagnosis, *systemic* treatment (hormonal or chemo-therapies) and surgery have improved the prospects for women with localised disease. Nevertheless, a significant percentage of these patients will relapse to more advanced invasive, *metastatic* disease. Currently available anti-tumoural therapies give little evidence of prolonged survival in metastatic or advanced breast cancer. The response rates for either hormonal or *cytotoxic* treatments are around 30%.

Phase II study of immunotherapy of advanced breast cancer by repeated intramuscular injection of recombinant vaccinia viruses containing sequences coding for human MUC-1 and IL2 (TG1031) - Department of Clinical Oncology, Guy's Hospital, London (GTAC 021)

1.22 The goal of this study is to stimulate the immune system to mount a specific anti-tumoural response against breast *adenocarcinoma*. This procedure is known as *immunoprophylaxis* or *immunotherapy*. The TG1031 vector is based upon the vaccinia virus, the live vaccine which has been used extensively in smallpox eradication programmes. TG1031 co-expresses both the MUC-1 and the IL2 genes.

1.23 Mucins are a family of glycoprotein molecules that are expressed on the surface of a wide variety of epithelia including reproductive tissue. Mucin 1 (MUC-1) has been shown to be abnormally expressed in approximately 90% of breast cancers as well as pancreatic, ovary and lung carcinoma tissue.

1.24 Interleukin 2 (IL2) is part of the panoply of chemical messengers used by the immune system to communicate between its various mainly cellular components. Experimental data has shown that IL2 is one of the major players involved in the recruitment/activation of sub-groups of T *lymphocytes* cells, involved in tumour destruction.

1.25 Co-expression of MUC-1 and IL2 is intended to recruit cytotoxic T cells to destroy tumour cells which have MUC-1 on their surface.

1.26 A phase I study involving the administration of the TG1031 vector to 7 patients took place in France. A summary of the initial findings in this trial was presented to GTAC.

1.27 In the phase II study at Guy's Hospital the investigators intend to evaluate as the primary objective, the response rate of patients with local/regional recurrent or metastatic breast cancer following administration of TG1031. The secondary objectives are to assess

TG1031 toxicity, immunological response and disease progression. A total of 33 patients with proven recurrent or metastatic breast adenocarcinoma expressing the MUC-1 antigen are to be recruited.

1.28 GTAC considered the protocol at its March 1997 meeting and approval was given subject to minor amendments.

OVARIAN CANCER

1.29 Ovarian cancers are a major cause of death for women in the United Kingdom. It was estimated that more than 6,000 new cases of ovarian cancer would be diagnosed in the UK, and 4,500 women would die from this disease in 1997.

1.30 Ovarian cancer is curable in its earliest stages[1], as it is highly responsive to chemotherapy. However an overwhelming majority of patients are diagnosed in the advanced stage. Death from ovarian cancer is largely due to early abdominal seeding of this *neoplasm* producing *carcinomatosis*. The mean survival rate of women with late stage ovarian cancer is five years. Over the last fifteen years the survival rate has only increased from 34% in 1975 to 39%.

[1] Stage I is where the tumour is limited to the ovaries, Stage II is when the tumour involves one or both ovaries with pelvic extension. Stage III is when the tumour involves one or both ovaries with microscopically confirmed peritoneal metastasis outside the pelvis and/or regional lymph node metastasis and Stage IV is distant metastasis that excludes peritoneal metastasis.

A multiple ascending dose study evaluating the safety and the gene transduction into malignant cells after the administration of E1A-lipid complex by intra-peritoneal administration in patients with epithelial ovarian cancer who over express HER-2/neu - A multicentre trial (GTAC 022)

1.31 Growth factor receptor signalling pathways are potentially important targets for anticancer therapy. The aim is to target and inhibit the activity of these factors. In recent years attention has focused on the use of the *proto-oncogene* HER2 (also called c-erbB2) encoding an epidermal growth factor (EGF) receptor related protein. The HER2/neu protein by contributing to the development of tumours may enhance metastatic potential in cancer cells.

1.32 Using a *liposome* vector this trial aims to block tumour development using a protein of viral origin.

1.33 The products of the E1A gene of adenovirus 5, a respiratory tract virus, have been shown to have an inhibitory effect on HER-2/neu expression in tumour cells *in vitro*.

1.34 The E1A gene will be complexed to a *lipid* carrier (similar to that used in the UK cystic fibrosis trials) and delivered by intraperitoneal injection to patients with epithelial ovarian cancer.

1.35 Between 12 and 24 patients, at 4 centres, whose tumours overexpress HER-2/neu, will receive the E1A-lipid complex in a repeated dose schedule.

1.36 The following centres will take part in the proposed research:

- The John Radcliffe Hospital, Oxford
- Guy's and St Thomas's Cancer Centre, London
- Royal Marsden Hospital, London.
- St George's Medical School, London.

1.37 GTAC reviewed this protocol at its September 1997 meeting and gave their approval subject to the provision of information on technical issues and the redrafting of the patient information sheets.

SECTION 2 - AMMENDMENTS TO PREVIOUSLY APPROVED PROTOCOLS/UPDATES

Genetic prodrug activation for breast cancer Imperial College School of Medicine, Hammersmith Hospital (GTAC/011)

2.1 The original protocol, approved by GTAC in October 1995[2], was to enrol up to 10 women with advanced breast cancer with skin involvement. This proposal sought permission to extend the patient group to include women with liver metastases. GTAC considered the amended proposal at its March 1997 meeting and considered that the proposed changes warranted full review. The Committee met with the proposers in June 1997.

2.2 GTAC has deferred its decision on the grounds that the increased risk to patients following genetic prodrug activation and repeated liver biopsies had not been sufficiently evaluated and that this increased risk, in relation to the possibility of direct benefit, as a result of repeated liver biopsies, had not been adequately communicated to patients. GTAC requested that the proposed work on patients with liver metastases should be submitted as a separate protocol. The proposer later withdrew their application to amend this trial.

Phase I trial of intra-tumoral injection with an E1B attenuated adenovirus, ONYX-015, into recurrent and locally advanced p53(-) squamous cell tumours of the head and neck - Beatson Institute, Glasgow (GTAC/014).

2.3 GTAC gave approval in January 1996[3] to a trial in which a modified adenovirus designed to selectively reproduce in, and kill, cancer cells was to be injected directly into the tumours of up to 30 patients with recurrent head and neck cancer.

2.4 During 1996 the proposers sought GTAC agreement to a number of trial amendments. These mainly included minor alterations to the clinical protocol and these were approved after postal circulation to members.

2.5 In May 1997, in the light of their findings in 27 head and neck cancer patients treated with ONYX-015, the proposers sought to extend the head and neck cancer study into a Phase 2 clinical trial in up to 30 evaluable patients. This was approved by Chairman's consent in July 1997.

2.6 At the end of 1996 the proposers contacted GTAC and requested to extend the study to patients with ovarian cancers. The Committee gave conditional approval to the recruitment of up to 24 patients with ovarian cancer in January 1997. In order to differentiate the patient groups, the ovarian cancer study is referred to as GTAC 014A.

2.7 A further protocol (referred to as GTAC 014B) was submitted in August 1997 - "A phase 2 trial of intravenous cisplatin, 5-FU and intratumoral injection with ONYX-015 into recurrent, chemotherapy naive squamous cell tumours of the head and neck". The protocol was initially discussed at the September 1997 meeting of GTAC and further information sought from the proposers. The trial was approved at the December 1997 meeting.

Multi-centre study of TA-HPV recombinant Vaccinia for Adjuvant Therapy of Early Stage Cervical Cancer - at St Mary's Manchester and University Hospital of Wales, Cardiff (GTAC 012B)

2.8 This proposal is to enhance the recognition of HPV E6 and E7 proteins in cervical carcinomas, using a vaccinia based vector (TA-HPV) thus offering the possibility of recruiting the patients immune system into the destruction of tumour cells.

2.9 This approach was pioneered in the UK and approved by GTAC in June 1995[2]. The objectives of the original trial were to establish the safety as well as the immunogenicity of TA-HPV in eight patients with late stage cervical cancer. (GTAC 012)

2.10 GTAC gave approval in May 1997 to recruit early stage cervical cancer patients (CIN3).

2.11 In the current multicentre proposal GTAC gave approval in August 1997 for a repeat vaccination study in early stage carcinoma, whereby following appropriate selection each patient could receive up to two vaccinations.

2.12 Initially it was intended to have three UK centres in Cardiff, Manchester and Cambridge participating, but the latter centre withdrew. This proposal is part of a wider European Organisation for Research in the Treatment of Cancer (EORTC) programme.

2.13 To collate information from the centres and report any adverse effects, a biological safety committee was put in place.

UPDATES

2.14 Of the 26 gene therapy research protocols approved by GTAC or its predecessor, the Clothier Committee, since 1993, a total of 155 patients have been recruited (see Annex 7).

2.15 No serious adverse reaction has been reported to date. However, there were adverse events reported to GTAC, namely some swelling/blistering following TA-HPV administration due to the type of dressing used at the inoculation site (GTAC 012A). It was also reported in 1997 that flu like symptoms were associated with the administration of the Onyx-015 adenoviral vector in head and neck cancer trials (GTAC 014A).

2.16 GTAC expects to receive detailed reports on current trials during 1998.

SECTION 3 - PROTOCOLS STILL UNDER REVIEW AT THE END OF DECEMBER 1997

3.1 Three protocols on gene therapy research submitted to GTAC in 1997 remain under consideration. These are:

(i) A phase I/II study of hepatic artery infusion with wtp53-CMV-Ad in primary and metastatic malignant tumours.

(ii) Pilot Study of recombinant carcinoembryonic antigen (CEA) vaccinia virus with post-vaccination CEA peptide challenge in combination with 5-fluorouracil and folinic acid in the treatment of colorectal cancer.

(iii) Phase I study of intraperitoneal administration of a replication-deficient adenovirus carrying a nitroreductase gene in ovarian cancer patients.

SECTION 4 - GENERAL COMMENTS ON PROTOCOLS

4.1 Cancer research proposals have continued to dominate the number of protocols submitted for review. However 1997 marked two significant changes. Firstly GTAC approved its first UK multi-centre cancer trial. Secondly, proposals were submitted involving the use of a "combinational" approach whereby conventional anti cancer drugs such as cisplatin or 5-fluorouracil are used to enhance gene therapy activity.

4.2 The Committee is grateful to proposers for their patience and clarity in answering the questions put by members when the protocols were reviewed at its meetings.

4.3 All the proposers are to be complimented on the way in which they have responded to the requests for the additional information needed by the Committee to complete its review of each proposal.

4.4 GTAC will continue the practice of seeking advice as appropriate from its panel of expert advisers prior to consideration of protocols. It will widen the expert panel membership as necessary. The Committee wishes to record its thanks to the expert advisors for their invaluable contribution to its work.

4.5 During 1997 GTAC met its target of reviewing completed proposals within a 90 day period.

4.6 Dates for GTAC meetings during 1998 are:

25 February

8 June

15 July

21 October

9 December

SECTION 5 - GENE THERAPY: REGULATORY ISSUES

5.1 UPDATE ON GENETICALLY MODIFIED ORGANISMS (GMOs) DIRECTIVES

5.1.1. Council Directive 90/219/EEC on the Contained Use of Genetically Modified Micro-Organisms (GMMOs)

Council Directive 90/219 was adopted in 1990 and includes measures to protect human health and the environment from risks associated with activities involving GMMOs in "contained" conditions. These activities can range from basic research to industrial production.

A Common Position on a revised Directive, to reflect technical progress and increased scientific knowledge, and to promote a consistent and harmonised approach to risk assessment, was reached in December 1997. The European Parliament's Second Opinion is awaited; adoption of the Directive is expected by Autumn 1998, with implementation around March 2000.

5.1.2. Council Directive 90/220/EEC on the Deliberate Release of Genetically Modified Organisms (GMOs)

Council Directive 90/220 covers the human and environmental safety of releases and marketing of GMOs. It also establishes a single market for GMO products under Article 100a of the Treaty. Delays in procedural aspects, particularly in resolution of applications to market GMOs, and criticisms over lacking transparency of the decision-making process, led to a revised proposal being put forward by the Commission.

The Commission formally adopted the proposal in November 1997 and it is expected that an orientation debate on the Directive will take place at the June Environment Council.

5.2 EC DRAFT DIRECTIVE ON PATENTING - LEGAL PROTECTION OF BIOTECHNOLOGICAL INVENTIONS

The proposed Directive aims to harmonize European patent laws and clarify interpretation thus underpinning the confidence of industry and academia.

By establishing a clear legal framework for the protection of biotechnological inventions without prejudice to other legislation this Directive aims to harmonise patenting provision for biotechnology across the European Community. It is expected to lead to very little change to existing UK regulation and practice.

The Directive has been with the European Parliament since 9 March 1998. The Parliament should deliver it's second opinion by early June.

5.3 EC DRAFT DIRECTIVE ON GOOD CLINICAL PRACTICE IN CLINICAL TRIALS

The Commission has forwarded proposals for a Directive on Good Clinical Practice in the Conduct of Clinical Trials. There was a public consultation in the autumn of 1997. The latest draft, which is now under discussion in a Council Working Group and the European Parliament is broadly in line with current UK practice and will be supported by a number of guidelines. As the procedures in Member States often differ significantly, the guidelines will mainly, for each area covered, draw together in a single document, a summary of individual Member States requirements. This should provide a comprehensive guide to organisations wishing to conduct multi-national clinical trials.

5.4 EC DRAFT DIRECTIVE ON *IN VITRO* DIAGNOSTIC MEDICAL DEVICES

Political agreement on a common position was finally reached on the In Vitro Diagnostic Devices Directive (IVDD) at the Internal Market Council held on 27 November 1997. This followed nearly two years of negotiations. Final clearance of the text will be completed early in 1998 when it will be submitted to the European Parliament for second reading. The proposal to extend the Medical Devices Directive to include a restricted range of devices containing substances derived from human tissues has been removed from the IVDD. Further discussions on this are being taken forward under the UK Presidency.

In the latter half of 1997 the Commission decided to ban the use of certain animal material, known as Specified Risk Material, from 1 April 1998. The ban will affect some medical devices, cosmetics, foods and pharmaceuticals, but as presently drafted the Commission Decision includes exemption for IVDs. Both the Medicines Control Agency (MCA) and the Medical Devices Agency (MDA) are actively considering implementation of the Decision although at the time of writing the Agriculture Council has rejected the latest draft.

5.5 THE DATA PROTECTION BILL/EC DIRECTIVE ON DATA PROTECTION

The Data Protection Bill was introduced in January 1998 following "Data Protection consultation on the Government's proposals" 1 July 1997. It gives effect to the EC Directive on Data Protection whose main provisions Member States must implement by 24 October 1998. The Bill also strengthens the rights of individuals to be told how their information may be used and their rights in obtaining copies of the data. The Bill extends existing data protection legislation controls to certain manually held personal data and attaches conditions on the processing of information.

5.6 FREEDOM OF INFORMATION

In December 1997 the Government published a White Paper on freedom of information "Your Right to Know"[5]. The proposals include giving members of the public, subject to certain safeguards, a statutory right to know about information and records which the Government and its agencies hold. It will apply across the public sector and the right of access would apply to recorded information that the body concerned holds.

SECTION 6 - INTERNATIONAL DEVELOPMENTS

6.1 US - UPDATE ON RECOMBINANT DNA ADVISORY COMMITTEE (RAC)

In July 1996 the NIH Director published a Notice of Intent[6] which foresaw the end of RAC and that all approval activity be relinquished to the Food and Drugs Administration (FDA).

November 1996 saw a response[7] from the NIH Director to public opinion to that proposed, with counter-proposals which sought to: (i) retain RAC, while modifying its roles and responsibilities; (ii) continue discussion of novel human gene transfer experiments without RAC approval of individual human gene transfer; (iii) encourage regular gene therapy policy conferences (GTPC); (iv) maintain public access to human gene transfer clinical trial information.

On 14 February 1997, the NIH Director published a revised Notice of Proposed Actions[8]. The Notice of Proposed Actions was in response to further public opinion and in keeping with the NIH's Director's intent to increase the usefulness and productivity of public discussion of human gene transfer research.

During its March 1997 meeting RAC recommended further changes to the proposed action which included clarification on the relationship of RAC and GTPCs, Institutional Biosafety Committee approval requirements, the objective of a NIH Human Gene Therapy Database and Environmental Assessment.

On 31 October 1997[9] the NIH Director published a Notice of Actions Under the NIH Guidelines that finalised the proposals of 22 November, 1996. Under this notice, the NIH shall specifically: (i) relinquish all approval responsibilities for recombinant DNA experiments involving human gene transfer to the FDA, which holds statutory authority for such approval; (ii) continue NIH registration of human gene transfer protocols; (iii) continue RAC discussion of novel human gene transfer experiments without RAC approval of individual protocols; (iv) regularly convene GTPCs; and (v) enhance public awareness and access to human gene transfer clinical trial information.

The 1998 March meeting of the RAC will consider further proposals[10] affecting gene therapy supervision in the US.

6.2. SWITZERLAND - CHANGES TO GENE TECHNOLOGY LAWS

Switzerland has a number of laws and ordinances affecting gene therapy. They are administered at both national and cantonal levels. In 1997 amendments to the Law on Environmental Protection ("contained use" and "deliberate release" into the environment of genetically modified organisms) and the Law on Epidemics came into force. These are intended to strengthen the legal framework regulating gene technology.

A Federal Expert Commission for Biosafety was established by the Federal Council in January 1997. One of the tasks of this Commission will be to advise on gene therapy clinical trials.

6.3 GERMANY - WORKING GROUP ON GENE THERAPY

In Germany there is a considerable body of law regulating both patients in clinical trials and medicinal products. Of particular importance to gene therapy trials is the German drug law (Arzneimittelgesetz: AMG). The AMG law administered by the competent authority in each federal state or Länder makes provision for clinical trial regulation. Marketing authorisation for gene therapy drugs is obtained by the European Commission via the EMED based on Council Regulation (EEC) No. 2309193.

During the past three years the Länder authorities and the Ministry of Health have been meeting to discuss gene therapy oversight. A report of their findings will be published in 1998 in the German Ministry's Official Journal (Bundesanzeiger).

In 1993 a commission for "Somatic Gene Therapy" was formed under the auspices of the German Medical Association. Based on the "Guidelines for Gene Transfer into Human Somatic Cells" published by the German Medical Association ("Deutsche Aerzteblatt 92, Heft 11, 16. Maerz 1995 (57), B-583 ff), this commission will, upon request, give advice to the local ethics committees on questions relating to gene therapy. An appraisal from the local ethics committee has to be obtained before initiating a clinical trial using gene therapy drugs according to the German drug law. In addition, documents including the pharmacological-toxicological data and the appraisal of the local ethics committee have to be presented to the competent federal higher authority, which is either the Paul-Ehrlich-Institut in Langen or the Federal Institut for Drugs and Medical Devices (BfArM) in Berlin.

6.4 NETHERLANDS - REPORT OF THE GENE THERAPY COMMITTEE OF THE HEALTH COUNCIL

On 4 June 1997 the Gene Therapy Committee of the Health Council presented to the Dutch Minister of Health its report[11] on the current state of gene therapy activity in the Netherlands. This comprehensive report makes several recommendations for changes to gene therapy regulatory oversight and makes an urgent plea to define more detailed regulation on quality control issues for biological products used as human therapeutics, argues for greater streamlining and transparency in the review of gene therapy protocols and calls for the establishment of an interdepartmental/inter-ministerial working group to pool and coordinate resources.

SECTION 7 - BIOETHICS

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7.1 Shared technology has often led to the globalisation of certain values and it is appropriate that in the field of human genetics, countries should work together towards the recognition of common ethical frameworks. In 1997, there were a number of developments in this area:

(i) In November 1997, UNESCO adopted the Declaration on the Human Genome and Human Rights[12], noting that research on the human genome and the resulting applications offer vast prospects for progress in improving the health of individuals and mankind, but emphasising that such work needs to fully respect dignity, freedom and human rights. The Declaration contains principles prohibiting unjustified discrimination, emphasising principles of consent and confidentiality, and encouraging the development of educational activities to improve awareness of the implications of developments in genetics.

(ii) The Council of Europe Convention on Human Rights and Biomedicine was opened for signature in April 1997. A protocol[13] prohibiting the cloning of human beings was opened for signature in January 1998 and further protocols on genetics, medical research, organ transplantation and the protection of the embryo and fetus are being developed.

(iii) The European Commission has replaced its Group of Advisors on the Ethical Implications of Biotechnology and has established a European Group on Ethics in Science and New Technologies, a multidisciplinary group of 12 members who will advise the Commission on all ethical questions relating to science and new technologies. It will commence work in 1998.

SECTION 8 - GTAC WORKSHOP

GENE THERAPY - MYTH AND REALITY: HYPE AND PRACTICALITY[1]

8.1 The Workshop

This one day Workshop was held on 21 March 1997 at Colindale, London. The objectives of the Workshop were to:

(i) look at what had been achieved in the first six years of gene therapy, what might be achievable over the next equivalent period and what might be seen as potential barriers to development.

(ii) identify a range of issues which GTAC might take forward in Committee discussion, by further consultation or by smaller follow-up workshops.

It was hoped that the output from such a Workshop would be of potential value to Health Departments, the Medicines Control Agency, healthcare professionals and the wider public.

8.2 The speakers/rapporteur

Given an outline remit of exploring the progress made in gene therapy so far, how the technology may develop and the potential barriers to progress, speakers were asked to present from a variety of perspectives.

The morning session was chaired by ***Professor John Durant*** (Science Museum and Imperial College), following an introductory presentation by the GTAC Chairman, ***Professor Norman Nevin.*** The issues of scientific and clinical progress were explored by ***Professor Nelson Wivel*** and ***Dr Martin Gore.*** After the morning coffee break, matters relating to public perception of genetics as a whole were discussed by the morning chairman.

Dr David King, editor of GenEthics News, opened the afternoon session chaired by ***Professor Elizabeth Anionwu*** (Institute of Child Health). Dr King discussed some of the social and ethical considerations raised by gene therapy. ***Professor Alan Kingsman*** from Oxford BioMedica talked of the commercial challenges of taking gene therapy from the bench, into the clinic and on to the market. ***Mrs Rosie Barnes*** (Cystic Fibrosis Trust) spoke of the expectations that patients and the Trust have of gene therapy technology.

The meeting concluded with both the morning and afternoon speakers taking part in panel discussions with the workshop participants before the Chairman invited ***Professor Anthony Dayan*** to summarise the points raised during the day's discussions (see Issues Arising).

8.3 Participants

Ninety eight people registered for the Workshop which on the day attracted around 80 people. Input came from the following "groups":

Molecular biologists developing the pre-clinical science.
Those clinicians with experience of gene therapy trials.
"Public" funding bodies - Medical Research Charities.
Local Research Ethics Committees.
Commercial interests.
Media - both general and professional.
Consumers - patients participating in gene therapy, patients' interest and support organisations.
Trust Hospitals and Health Authorities involved in studies.

[1] A copy of the full Proceedings Document can be obtained from the Department of Health Homepage on http://www.open.gov.uk/doh/genetics/htm.

8.4 Issues Arising

The issues identified as being particularly pertinent to gene therapy were divided by Professor Dayan into two main categories: (a) Technical and Scientific and (b) Ethical, Social and Political.

8.4.1 Technical and Scientific issues

(i) Criteria justifying clinical work:

- Which patients may be eligible
- What diseases may be candidates
- Safety, Efficacy, Quality

(ii) Germ line effects.

(iii) Identification of who directs and controls gene therapy

(iv) How should gene therapy be developing in a regulated world? Who regulates what, how and why?

8.4.2 Ethical, Social and Political

(v) Criteria for ethical committee approval of the trial. How these should evolve?

(vi) What are the responsibilities of:

- Scientists/Clinicians
- Other health professionals
- The public
- The "Media"

How would these responsibilities be met?

(vii) Will there be a case for germ line gene therapy. Should such interventions be permitted or prevented?

(viii) Can "enhancement" therapy be permitted or should it be prevented?

(ix) The high cost of developing therapeutic products and their availability to a relatively small market. This is a particular issue in the rarer inherited single gene disorders. Who should provide funds and who should be rewarded?

8.5 Feedback from Participants

Overall the Workshop was assessed as "successful" in terms of its objectives.

Specific suggestions for future events included:

More discussion time needed;

More discussion of economic and legal issues;

A pan-European meeting on similar lines;

"Break out" sessions would help;

More detail on the outcome of trials to date;

A glossary of "technical terms" in the advance papers.

Discussions should have been more focused on either science/technology issues or on ethics/public perception issues.

8.6 Potential Outcomes and Follow up events

As mentioned in the objectives section the output from the Workshop should be of value to a wide spectrum of public and professionals. Apart from the publication of the proceedings document and articles in the specialist press, follow-up workshops are envisaged. For example the question of prevention of transmission to the germ line was identified as an specific issue.

SECTION 9 - REFERENCES

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[6] Notice of Intent to Propose Amendments to the NIH Guidelines for Research Involving Recombinant DNA Molecules Regarding Enhanced Oversight of Recombinant DNA Activities July 8, 1996, Vol 61: No. 131: 35774-35777.

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[10] Notice of Proposed Actions Under the NIH Guidelines for Research Involving Recombinant DNA Molecules Federal Register: February 11, 1998 Vol 63, No. 28.

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SECTION 10 - GLOSSARY

Adenocarcinoma

A tumour of glandular and connective tissue; it often has the structure and the function of the parent tissue.

Ascites

An abnormal accumulation of fluid in the abdominal cavity.

ADA deficiency

An inherited disease, due to a faulty gene, in which there is a lack of the gene product, the *enzyme* adenosine deaminase.

Adenoviral/Adenovirus (see virus)

A DNA contained virus causing mild upper respiratory tract infection.

B cell

A type of white blood cell important in immunity.

Body cell (somatic cell)

The non-germ line cells of the body. Genetic change in these body cells affect only the individual not individuals of succeeding generations.

Carcinomatosis

A pathological condition which gives rise to the development of tumours.

Cationic lipid (see liposome)

Cell (see also: body cell, germ line cell, somatic cell)

The smallest unit of living organisms which, given the right conditions, can survive independently and reproduce itself. It has been estimated that the body of a human adult comprises 50 million million cells.

Coding, codes

Refers to the sequence of base pairs on the DNA which contain genetic information to produce a protein product.

Cytotoxic/cytopathic

The ability of an agent to injure a living cell.

DNA (deoxyribonucleic acid)

The chemical substance in chromosomes and genes in which genetic information is coded.

Enzyme

A protein which acts as a catalyst in the body's many chemical reactions. A deficit in the production of an enzyme or its function may result in an inherited disorder of *metabolism*.

Expression (see gene expression)

Gene

A part of the DNA molecule of a chromosome which directs the synthesis of a protein.

Gene expression

The production by a cell of the protein for which the specific gene codes.

Gene therapy

Used without qualification means the genetic modification of body cells of an individual patient, directed to alleviating disease in that patient.

Genetic diseases or disorders

Conditions which are due to defects in the genetic endowment of an individual. They may be the direct consequences of defects in single genes; or in whole chromosomes, parts of which may be lost, duplicated or misplaced; or due to the interaction of multiple genes and external factors in fetal development. Later in life such interactions appear to be the basis of many of the common serious disorders, such as heart disease, diabetes and cancer.

Germ line cells

The cells of the body which transmit genetic information to the next generation. They are the sperm in males and ova in females.

Germ line gene therapy

Gene therapy which seeks to introduce or modify genes in germ line cells. The effect of such a modification would be transmissible to descendants.

Immuno-modulation

Modifying the body's immune response eg. recruiting of *lymphocytes* to recognise cancer cells.

Immunoprophylaxis (see immuno-modulation)

Immune response

A specific white blood cell or antibody response to "foreign" protein

Immunotherapy (see immuno-modulation)

Lipid

A fatty substance.

Liposome

A fatty droplet containing DNA which can enter a cell carrying the genes needed for gene therapy.

Lymphocyte

A type of white blood cell important in immunity.

Lysis, lytic, lyse

The disruption or dissolution of cells or cellular material by chemicals, physical agents, enzymes or some micro-organisms.

Metabolism

Describes the chemical reactions taking place within the body. These reactions are necessary for its maintenance and growth.

Metastatic, metastases

Disease, usually cancer, that has spread from one site to another unconnected organ.

Molecular biology

The study of proteins and *nucleic acids*, substances that make up the living world, their structures and their relationship to biochemical activity; and the substances that are the repositories of genetic information and the agencies for its communication from one generation to the next.

Murine

Of mouse origin.

Mutation, mutant

A molecular change in which DNA is altered with genetic consequences. A gene which has undergone mutation is called a mutant; so also is an organism in which the mutant gene is expressed.

Neomycin (neo)

An antibiotic which can be used as a label for gene transfer.

Neoplasm

New formation of tissue; a tumour.

Nucleic acid

DNA is a type of nucleic acid. A more specialised type of nucleic acid is called RNA which is the genetic material of some viruses such as *retroviruses*.

Neural, Neurological

Characterised by or pertaining to nerve cells.

Palliative Treatment

Treatment whose principal aim is to lessen the symptoms and discomfort the patient may experience during illness.

Plasmid

A small piece of DNA, usually of bacterial origin, capable of reproducing in bacterial cells and carrying genes. Plasmids are used in some gene therapy trials in place of virus vectors or liposomes.

Prodrug

Relatively inert compounds that are converted to an active or toxic form in the body.

Proliferative diseases, Proliferation

Diseases caused by the deregulated multiplication of cells within the body.

Promoter

A DNA sequence which controls genes. Alterations in the promoter may alter the level of gene expression.

Prophylaxis

Methods of preventing disease or preventive treatment.

Protein

Proteins are essential constituents of the body. They form the structural materials of muscles, tissues, organs and are regulators of function, as enzymes and some hormones. Proteins are coded for by DNA.

Proto-oncogene

Genes found in normal cells which control cell division. There is evidence to suggest that certain cancers are caused by the activation (switching on) of these genes.

Recombinant DNA

Using modern scientific techniques it is possible to make alterations to DNA in the laboratory. Genes can be removed, relocated or added, changing the sequence of genes. Such modified DNA is called recombinant.

Retrovirus

A type of virus often used in gene therapy as a vector. Such viruses are usually animal viruses rather than agents of human disease. They are made safe so that they can enter a human cell carrying a gene for gene therapy without causing disease.

Somatic cell (see body cell)

Shunt

A diversion; particularly a diversion of blood due to congenital defects, pathological processes or surgical procedures.

Systemic

Relating to the body as a whole, rather than its individual parts.

Tumourigenicity, Tumourigenesis

A process describing the origin or development of tumours.

Tumour suppressor genes

The protein product of a gene that regulates the multiplication of cells. The absence or dysfunction of a tumour suppressor gene is associated with the production of cancer cells.

Vaccinia virus

This is a vaccine strain of virus. Live vaccinia virus has been used extensively in smallpox eradication programmes.

Vector(s)

In most situations, a new gene cannot be added to human cells without being transported into the cell in some form of a carrier (vector) - usually a virus, a liposome or a plasmid.

Virus

A tiny infectious organism, too small to reproduce outside a host cell. Viruses carry nucleic acid surrounded by protein. Some viruses cause disease, eg chicken pox, influenza, others however, suitably modified, can be used as a means of delivering genes into cells.

Xenogenic

To describe material of non-human origin from another animal species eg xenotransplantation, organ transplants from another species.

ANNEX 1 - GTAC TERMS OF REFERENCE

The terms of reference of the Gene Therapy Advisory Committee (GTAC) are:

(1) to consider and advise on the acceptability of proposals for gene therapy research on human subjects, on ethical grounds, taking account of the scientific merits of the proposals and the potential benefits and risks;

(2) to work with other agencies which have responsibilities in this field including local research ethics committees and agencies which have statutory responsibilities - the Medicines Control Agency, the Health and Safety Executive, and the Department of the Environment;

(3) to provide advice to UK Health Ministers on developments in gene therapy research and their implications.

The Committee will have a responsibility for:

(a) providing advice for applicants on:

  (i) the content of proposals, including the details of protocols, for gene therapy research on human subjects;

  (ii) the design and conduct of the research;

  (iii) the facilities necessary for the proper conduct of the research;

  (iv) the arrangements necessary for long term surveillance and follow up.

(b) receiving proposals from doctors who wish to conduct gene therapy research on human subjects, and making an assessment of:

  (i) the clinical status of the subjects;

  (ii) the scientific quality of the proposal;

  (iii) the scientific requirements and technical competence necessary for carrying out gene therapy research effectively and safely;

  (iv) whether the clinical course of the particular disorder is known sufficiently well for

    - sound information, counselling and advice to be given to the subject (or those acting on behalf of the subject);

    - the outcomes of therapy to be assessable;

  (v) the potential benefits and risks for the subject of what is proposed.

ANNEX 2 - MEMBERSHIP OF GTAC

Chairman

Professor Norman C Nevin BSc, MD, FFPHM, FRCPath. FRCP Ed, FRCP
Department of Medical Genetics
Belfast City Hospital

Members

Professor Elizabeth Anionwu, PhD, RGN, HV
Dean of Nursing,
Wolfson School of Health Sciences
London

Mrs Rosemary Barnes
Chief Executive, Cystic Fibrosis Trust
Kent

Professor John Burn MD, FRCP
Northern Genetics Service
Royal Victoria Infirmary
Newcastle

Professor Anthony Dayan MD, FRCP, FRCPath, FFPM, FIBiol
St Bartholomew's & The Royal London School of Medicine & Dentistry
Department of Toxicology
London

Reverend Dr Keith Denison MA, PhD
The Church in Wales
Diocese of Monmouth

Dr Brenda Gibson FRCP, FRCPath, DFM
Department of Haematology
Hospital for Sick Children
Glasgow

Professor Ian Hart BVSC, MRCVS, PhD, FRCPath
United Medical & Dentistry Schools
of Guy's and St Thomas' Hospitals
London

Mrs Ann Hunt
Tuberous Sclerosis Association

Professor Theresa Marteau MSc, PhD, CPsychol
Psychology & Genetics Research Group
Guy's Campus, London

Professor James Neil BSc, PhD, FRSE
Department of Veterinary Pathology
University of Glasgow Veterinary School

Professor Anthony Pinching DPhil, FRCP
Department of Immunology - Smithfield
St Bartholomew's and The Royal London School of Medicine & Dentistry
Queen Mary & Westfield College
London

Miss Eleanor Platt QC
The Temple
London

Sir Brian Richards CBE, BSc, PhD
Peptide Therapeutics Group
Cambridge

Professor C Michael Steel MB, ChB, PhD, DSc, FRCP Ed, MRCPath
School of Biological & Medical Sciences
University of St Andrews

Mrs Irene Train RGN, RM, RHV, QIDN
Formerly Director Public Health Nursing
Clwyd Health Authority

New Member 1997

Professor Patrick Johnston MRCI, MB, BCh, BAO
Department of Oncology
Belfast City Hospital

Observers

Dr Elaine Gadd
Department of Health
London

Dr Amanda Goldin
Human Genetics Advisory Commission
Office of Science and Technology

Dr Brian Davis MRCP
Medicines Control Agency
London

Dr Lincoln Tsang
Medicines Control Agency
London

Secretariat

Mr Anthony J Taylor
Dr Veronica Lecomte
Dr Nick Saunders*
Mrs Margaret Straughan
Mr Mark Noterman

* (seconded from Central Public Health Laboratory Colindale, London. August-December 1997)

ANNEX 3 - REGISTER OF MEMBERS INTERESTS

GTAC members have declared the following personal share holdings or funding from the biotechnology/pharmaceutical industry.

Professor Norman C Nevin	None
Professor Elizabeth Anionwu	None
Mrs Rosemary Barnes	Director, Association of Medical Research Charities Non-Executive Director, Greenwich Healthcare Trust Non-Executive Director, Greenwich Building Society (now Portman Building Society)
Professor John Burn	Clinical Advisor, Therexsys PLC
Professor Anthony Dayan	Consultancies: Cantab, Fournier, Introgene, Schering Plough and Therexsys PLC
Reverend Dr Keith Denison	None
Dr Brenda Gibson	None
Professor Ian Hart	None
Mrs Ann Hunt	None
Professor Patrick Johnston	Research grant from Bristol Myers Squibb Consultancy, Eli Lilly
Professor Theresa Marteau	None
Professor James Neil	Research grant from Intervet International BV Ad hoc consultancy, Q-One Biotech
Professor Anthony Pinching	Infrequent consultancies with Roche, Pharmacia Upjohn, Glaxo Wellcome. Travel sponsorship from Boehringer Ingelheim and Glaxo Wellcome.
Miss Eleanor Platt QC	Personal Shareholder in SmithKline Beecham, Glaxo Wellcome and Smith & Nephew Associated Companies
Sir Brian Richards CBE	Chairmanship, Oxford BioMedica Chair of Peptide Therapeutics Group PLC, Alizyme PLC, and CeNeS Limited Board member of Innogenetics BV, ICRT and Prelude Trust PLC
Professor C Michael Steel	None
Mrs Irene Train	None

ANNEX 4 - EXTERNAL EXPERT ADVISERS TO GTAC

During 1997 GTAC sought the views of the following expert advisers during the review of protocols submitted to the Committee.

Professor Sir Roy Calne, Department of Surgery, University of Cambridge

Professor Derek Crowther, CRC, Manchester

Dr Huw Davies, Division of Life Sciences, King's College, London

Dr Richard Gopal, Enteric and Respiratory Virus Laboratory, Central Public Health Laboratory, Colindale, London

Professor Don Jeffries, Department of Virology, St Bartholomew's & Royal London School of Medicine & Dentistry

Dr Nicholas Jones, ICRF, Lincoln Inn Fields, London

Dr Jonathan A Ledermann, Department of Oncology, UCL, London

Professor Nicholas Lemoine, ICRF, Hammersmith Hospital, London

Professor Pedro Lowenstein, Department of Medicine, University of Manchester

Professor Neil McIntyre, Royal Free Hospital, London

Professor Anthony Minson, Division of Virology, Cambridge University, Cambridge

Professor Robert Souhami, UCL Medical School, London

Dr M M Van de Eb, Department of Surgery and Department of Medical Biochemistry, Lieden, The Netherlands

Dr Maria Zambon, Enteric and Respiratory Virus Laboratory, Central Public Health Laboratory, Colindale, London

ANNEX 5 - HERPES SIMPLEX VIRUS EXPERT SUBGROUP

Members of the GTAC Herpes Simplex Virus Expert Subgroup are:

Professor Norman C Nevin (Chairman)
Department of Medical Genetics
Belfast City Hospital

Professor Pedro Lowenstein
Department of Medicine
University of Manchester

Professor Anthony Minson
Division of Virology
Cambridge University

Professor Don Jeffries
Department of Virology
St Bartholomew's & Royal London School of Medicine & Dentistry

ANNEX 6 - NEW EMERGING TECHNOLOGIES SUBGROUP

Members of the GTAC New Emerging Technologies Subgroup are:

Reverend Dr Keith Denison (Chairman)
The Church in Wales
Diocese of Monmouth

Mrs Rosemary Barnes
Chief Executive
Cystic Fibrosis Trust
Kent

Dr Brenda Gibson
Department of Haematology
Hospital for Sick Children
Glasgow

Professor Ian Hart
UMDS
St Thomas' Hospital
London

Mrs Ann Hunt
Tuberous Sclerosis Association

Professor C Michael Steel
School of Biological & Medical Sciences
University of St Andrews

Mrs Irene Train
Formerly Director Public Health Nursing
Clwyd Health Authority

Co-opted Members to work on gene therapy *in utero*:

Dr C Casimir
Imperial College School of Medicine
London

Dr David Liu
City Hospital
Nottingham

ANNEX 7 - GENE THERAPY RESEARCH 1993 – 1997

#Protocol	Details	Centre	Outline Approval	Trial Commenced	Vector/ gene	Packaging cell line	No. of Patients
001 CLOSED	SCID-ADA	Institute of Child Health / Great Ormond Street Hospital	1-93	3-93	pLGAL	pOAM-P1	1
002 CLOSED	CF Nasal trial	Royal Brompton	3-93	9-93	Liposome DC-Chol/CFTR	-	15
003	B-cell lymphoma immunoglobulin	MRC Cambridge	7-93	11-94	pVAC1/anti-idiotype	-	7
004	Neuroblastoma	ICRF Bristol	2-94	Trial withdrawn	LNL-6/neo G1N-neo	PA317	-
005	Metastatic melanoma	ICRF Oxford	5-94	6-95	pNASSB-BGal pNASSB-IL2	-	13
006 CLOSED	Metastatic melanoma	Institute of Cancer Research /Royal Marsden Hospital	2-94	10-94	MFG-S-IL2	GP+env AM12	12
007 CLOSED	CF Nasal trial	Oxford/Cambridge	2-94	5-95	Liposome DC-Chol/CFTR	-	12
008 CLOSED	CF Nasal trial	Edinburgh	5-94	6-95	Liposome DOTAP-CFTR	-	16
009	CF lung trial	Royal Brompton Hospital	9-94	-	Liposome DC-Chol/CFTR	-	-
010 CLOSED	Lymphoma	University College London Medical School	12-94	10-95	pHaMDR-1	AMI2M1	3
011 CLOSED	Breast Cancer	Hammersmith Hospital	10-95	10-95	pERCY	-	12

#Protocol	Details	Centre	Outline Approval	Trial Commenced	Vector/ gene	Packaging cell line	No. of Patients
012	Cervical Carcinoma	University of Wales, Cardiff	6-95	9-95	TA-HVP	-	1+8
012A	Cervical intraepithelial neoplasia III	University of Wales, Cardiff	5-96	9-96	"	-	12
012B	Cervical Cancer	University of Wales, Cardiff/University of Manchester	8-97	1-98	"	-	1
013	Hurlers Syndrome	Royal Manchester Children's Hospital, Manchester	12-95	5-97	pLX	GP+env AM12	3
014	Head and Neck Cancer	Beatson Oncology Centre, Glasgow	1-96	3-96	Onyx-015	Human Kidney cell line 293	19
	Head and Neck Cancer Phase II Study	Beatson Oncology Centre, Glasgow	7-97	7-97	"	"	7
014A	Recurrent/Refractory ovarian cancer	Beatson Oncology Centre, Glasgow	2-97	3-97	-	-	6
015	CF Nasal Trial	Oxford/Cambridge /Leeds/Manchester Consortium	5-96	7-96	Liposome DC-Chol/ CFTR	-	11
016 CLOSED	Head and Neck Cancer	Institute of Cancer Research Royal Marsden Hospital	9-96	12-96	SCH 58500	Human embryonic Kidney cell line 293	-
017 CLOSED	CF Lung and Nasal Trial	Royal Brompton Hospital	11-96	11-96	pCF1-CFTR # 67		16
018	Glioblastoma	Beatson Oncology Centre, Glasgow	12-96	10-97	HSVI ICP 34.5-1716	BHK 21/C13	3

#Protocol	Details	Centre	Outline Approval	Trial Commenced	Vector/ gene	Packaging cell line	No. of Patients
019	Glioblastoma	Beatson Oncology Centre, Glasgow Institute of Neurological Sciences, Glasgow	3-97	Trial withdrawn	SDZGLI328 HSV-TK	PA317	-
020	Gatrointestinal cancer/ /malignant cancer ascites	Royal Marsden Hospital, London	4-97	Not yet started	Ad5CMV-p53	293 cell line	
021	Breast Cancer	Guy's Hospital, London	11-97	Not yet started	TG 1031	-	
022	Ovarian Cancer	The John Radcliffe Hospital, Oxford Guy's and St Thomas's Cancer Centre, London Royal Marsden Hospital, London. St George's Medical School, London.	9-97	1-98	E1A Lipid complex	-	2

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